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Familial Paraganglioma and Gastric Stromal Sarcoma: A New Syndrome Distinct From the Carney Triad

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Paragangliomas may be inherited in an autosomal dominant manner either alone (as in PGL1, PGL2, and PGL3 syndromes) or as a component of a multiple tumor syndrome (as in von Hippel-Lindau disease and neurofibromatosis type 1). In this article, we describe 12 patients (7 male and 5 female) with an average age of 23 years from five unrelated families that manifested paraganglioma and gastric stromal sarcoma; the tumors were inherited in an apparent autosomal dominant manner, with incomplete penetrance. Seven patients had paraganglioma, four had paraganglioma and gastric stromal sarcoma, and one had gastric stromal sarcoma. The paraganglioma was multicentric and the gastric stromal sarcoma multifocal. Because of the rarity of gastric stromal sarcoma and its multifocality, the young age of the patients, and the unlikelihood of coincidental co-occurrence of paragangliomas and gastric stromal sarcomas, we suggest that a new syndrome exists with these two main components, a condition that is familial and distinct from the Carney triad. Published 2002 Wiley-Liss, Inc.†

KEY WORDS: paraganglioma; gastric stromal tumor; syndrome; familial; Carney triad; pheochromocytoma; catecholamines

INTRODUCTION

In 1977, Carney et al. [1977] reported the association of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma, and pulmonary chondroma in two patients and two of the three tumors in five other patients, all unrelated young females. The pattern and age of tumor occurrence—multifocal lesions in multiple organs in young patients—suggested a heritable disorder. The association was subsequently referred to as the Carney triad [Grace et al., 1981; OMIM, 2001, #604287].

In 1999, Carney [1999] reported 79 cases of the triad, 67 female and 12 male patients. One-fifth of the patients had the three tumors, the remainder had two of the three, usually the gastric and pulmonary lesions. Adrenocortical adenoma was identified as a new constituent of the disorder, and esophageal leiomyoma as a probable component. Because of the rarity of the three original components, the presence of any two of them was considered sufficient for diagnosis of the association, particularly if the tumors were multifocal and the patient a young female.

Intriguingly, 2 of the 79 patients, a young woman and a young man, each with two elements of the triad (gastric sarcoma and paraganglioma), had a sibling with one element (paraganglioma), raising the possibility that the triad might be a familial condition. The inheritance of the disorder if it was heritable remained unclear because none of the 355 primary relatives (parents, siblings, and children) of the remaining 77 patients had manifested any of the components.

This article describes the findings in the two siblingships and those in three other kindreds with apparent familial occurrence of paraganglioma and gastric stromal sarcoma. From these observations, we identified a familial syndrome of paraganglioma and gastric stromal sarcoma that appears to be distinct from the Carney triad.

MATERIALS AND METHODS

We studied five families, one of which had attended the Mayo Clinic [Walker and Dvorak, 1986; Tortella

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et al., 1987; McCaffrey et al., 1994]; the other cases were communicated to one of us (J.A.C.) by their families' physicians. A genetic history encompassing at least four generations was obtained for each family. Available clinical, surgical, and pathologic reports from affected family members were reviewed. Histologic slides and paraffin blocks with samples of their tumors were reassessed. For immunocytochemical study, 5 micron thick sections of formalin-fixed, paraffin-embedded tumor were deparaffinized and exposed to antibodies against chromogranin, actin, desmin, c-KIT, and CD34.

RESULTS

Twelve patients, seven male and five female, were studied from five unrelated families (Fig. 1). The families had a European ancestral background (German, French, Polish, and English); one family was Jewish. The pedigrees are shown in Figure 1. Selected findings among the patients are presented in Table I. Of the 12 patients, seven had paraganglioma, four had paraganglioma and gastric stromal sarcoma, and one had gastric stromal sarcoma. A diagnosis of the Carney triad had been made for the four patients with both tumors [Colwell et al., 2001]. No patient had a pulmonary tumor.

Paraganglioma

Eleven patients (92%), ranging in age from 10 to 61 years (mean, 33 years), had 28 paragangliomas excised. Two paragangliomas were not removed; one was irradiated and the other embolized. The tumor was a symptomless mass in eight patients; it caused hypertension in three patients who were young (10, 14, and 18 years) and who had retroperitoneal, extra-adrenal neoplasms. The paraganglioma was multicentric in eight patients and single in three. The tumor developed in the neck (intercarotid paraganglia, 15 neoplasms; intravagal paraganglia, 2; and jugular paraganglia, 1), retroperitoneum (aorto-sympathetic paraganglia, 9), mediastinum (aortico-pulmonary and superior mediastinal paraganglia, 1 each), and adrenal medulla (1). One patient had six paragangliomas (neck, mediastinum, and abdomen, adrenal and extra-adrenal). Four whose initial paraganglioma had been nonfunctioning subsequently had a functioning tumor (three in the retroperitoneum, extra-adrenal; one in the mediastinum). In four patients, a vascular crisis developed during manipulation or removal of the tumor (hypertension in three; hypotension in one). Two tumors that were considered recurrent were irradiated.

The urinary content of catecholamines and their metabolites was elevated in five of seven patients. Results of a regitine (phentolamine mesylate) test were positive in one of two patients. The neoplasms were localized using various methods, including retroperitoneal pneumoroentgenography (two patients in the 1960s), computed tomography, magnetic resonance imaging, angiography, and radioactive iodine-metaiodobenzylguanidine scanning.

Grossly, the paragangliomas ranged in size from $1.5 \times 1.4 \times 0.9$ cm to $6 \times 6 \times 3$ cm (Fig. 2, top). All were encapsulated or circumscribed except for one carotid body tumor that extended to the margin of resection

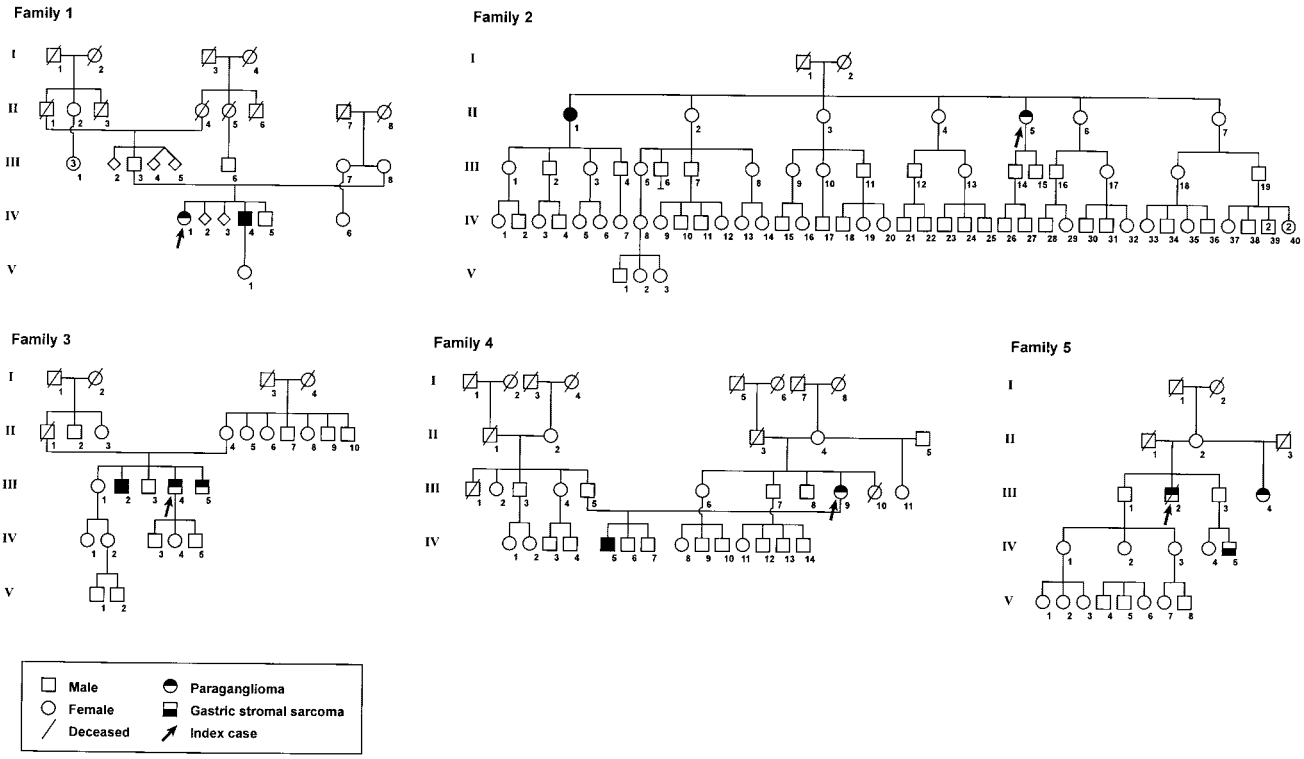

Fig. 1. Pedigrees of five families.

TABLE I. Selected Findings in 12 Patients From Five Families*

Patient identification	Sex	Presentation		Tumors of PG-GSS syndrome		Other findings	Status	
		Age, years	Tumor	PG	GSS		Age, years	Comment
Family 1								
IV.1	F	20	PG	m, nf		Normal external genitalia	35	Alive; bilateral etroperitoneal masses
IV.4	M	16	GSS	m, nf	Multiobulated	Pigmented penile spots, Horner syndrome	33	Alive; residual embolized PG
Family 2								
II.1	F	21	PG	m, f	m, met	Forearm soft-tissue mass	66	Alive; recurrent GSS
II.5	F	14	PG	m, f			58	Well
Family 3								
III.2	M	46	PG	m, f	m, met	Colon polyps	59	Well
III.4	M	40	PG	m			53	Alive; glomus jugulare PG
III.5	M	10	PG	m, f		Basal cell carcinoma	48	Alive; multiple PG
Family 4								
III.9	F	18	PG	f		Basal cell carcinoma	46	Well
IV.5	M	9	GSS	nf	m		18	Alive
Family 5								
III.2	M	23	PG	m, f			46	Dead; intracranial PG and aspiration pneumonia
III.4	F	31	PG	nf			59	Well
IV.5	M	16	GSS		m, met		26	Alive

*PG, paraganglioma; GSS, gastric stromal sarcoma; m, multiple; f, functioning; nf, nonfunctioning; met, metastatic.

(the neoplasm did not recur within 13 years of follow-up). The original diagnosis of paraganglioma (Fig. 2, bottom) was confirmed microscopically for all cases. The tumors were chromogranin-positive by immunocytochemistry. Two encapsulated carotid body tumors recurred. No paraganglioma metastasized. During evaluation for bilateral carotid body tumors, a mass thought to be another paraganglioma was found in the left retroperitoneum of a 20-year-old patient (family 1, IV.1). It was recommended that the mass be removed surgically but the patient did not return for the procedure. Three years later, a similar contralateral lesion was found. The size of the tumors (the largest, $3 \times 2.8 \times 1.4$ cm) did not change during the next 5 years. The urinary content of catecholamines was normal. The patient did not wish further investigation or treatment and is symptomless at age 35 years.

Surgical complications of removal of the tumors included hemiplegia (after resection of portions of the external and internal carotid arteries; 1 patient), hoarseness (three patients, one of whom also had dysphagia), and unilateral paralysis of the tongue (one patient).

Gastric Stromal Sarcoma

Five patients (42%) had gastric stromal sarcoma at ages ranging from 9 to 58 years (mean, 24 years). In two, investigation was prompted by severe anemia resulting from gastric ulceration and bleeding. Two other patients had mild anemia; in one, the neoplasm was found during investigation of the anemia; in the other, it was discovered incidentally during abdominal radiographic examination for suspected pheochromocytoma. The fifth patient had vague abdominal symptoms, intermittent fever, and a palpable epigastric mass. Gastric roentgenographic examination showed a lesion impinging on the posterior wall of the stomach. The tumor was the presenting lesion in three patients.

The sarcomas were treated by segmental gastric resections (one patient) and subtotal gastric resection (four patients). The patient who had the segmental resections (family 2, II.1) had her first gastric operation for separate tumors at age 22 years; additional gastric tumors developed at age 33 years, for which a radical subtotal gastric resection was performed; now, at age 66 years, she has a further recurrence in the gastric remnant. One or more nodules of suspected perigastric or omental metastasis were present at time of surgery in three cases.

The original pathologic diagnoses in the five cases were smooth muscle stromal tumor, leiomyoma and leiomyosarcoma (different diagnoses for separate tumors in one patient), epithelioid leiomyosarcoma, and gastric stromal sarcoma (two patients). Grossly, two or more tumors located on the lesser gastric curvature or in the distal stomach were present in four patients. The fifth patient had an exophytic multilobulated tumor (Fig. 3, top). The neoplasms ranged in size from 2 cm in

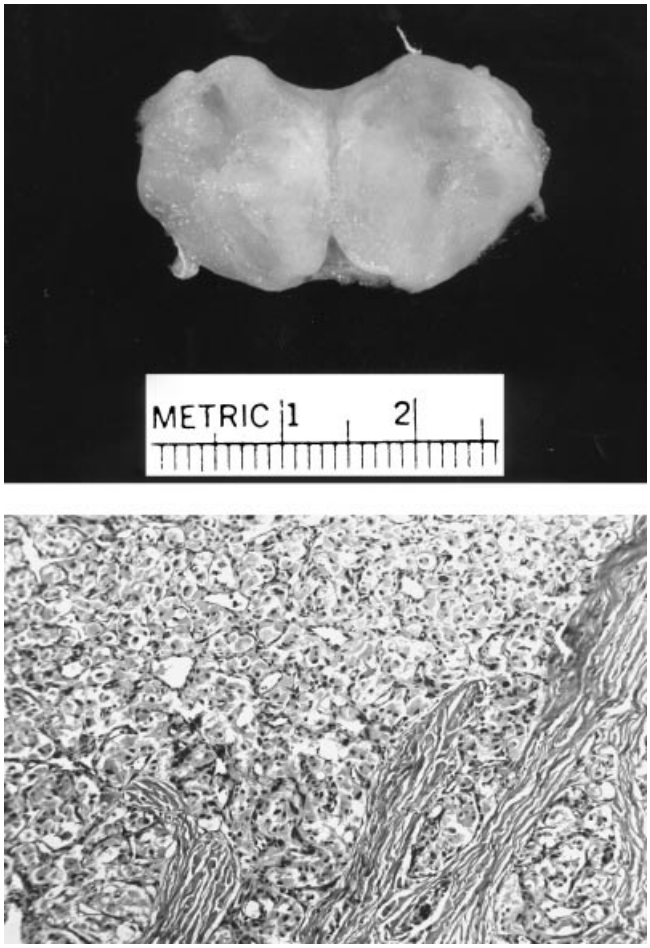

Fig. 2. Carotid body tumor (family 1, IV.4), **Top:** Glistening fleshy and white cut surface of sharply circumscribed left carotid body tumor. **Bottom:** Variably sized clusters of cells (Zellballen) and thick, fibrous bands typical of paraganglioma. (Hematoxylin and eosin; × 100).

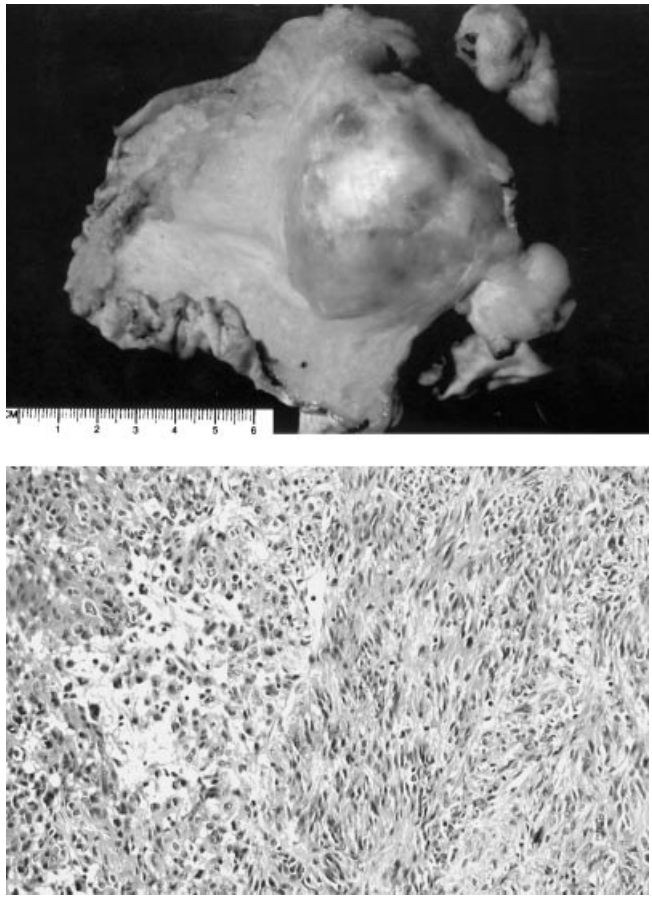

Fig. 3. Gastric stromal sarcoma (family 1, IV.4), **Top:** Exophytic, slightly lobulated mass protruding from the posterior wall of the stomach. **Bottom:** Juxtaposed populations of epithelioid cells (left) and spindle cells (right) with suggestive palisading of nuclei. (Hematoxylin and eosin; × 160).

diameter to $8 \times 7 \times 4.5$ cm. One or more tumors had caused mucosal ulceration in four patients.

Microscopically, the tumors were intramural and located primarily in the muscularis propria. All had the features of gastric stromal sarcoma, exhibiting polygonal and spindle cells (Fig. 3, bottom). Antibodies against c-KIT and CD34 stained the cells and those against actin and desmin did not (four of four patients). Metastasis to gastric lymph nodes (three patients) and peritoneum (two of the three patients) was verified.

Follow-Up

Eleven patients were alive; one was deceased (Table I). Two had untreated paraganglioma. Another two had residual treated paraganglioma (one tumor had been irradiated and the other embolized). One patient (family 1, IV.1) with bilateral retroperitoneal masses, probably paragangliomas, was asymptomatic. A patient (family 2, II.1) who had peritoneal metastasis from the gastric stromal sarcoma at age 33 had no evidence of abdominal dissemination at reoperation (for paraganglioma) at age 65 years. The deceased patient (family 5, III.2) succumbed at age 46 years to a combination of intracranial extension of a jugulotympanic paraganglioma and postoperative neurologic deficits after carotid body surgery, which resulted in an inability to swallow and secondary aspiration pneumonia. There was no autopsy.

Other Findings

One patient (family 2, II.1) who also has a forearm mass thought to be a lipoma had a symptomless posterior mediastinal mass at T9–10 level, which was discovered at age 17 years on routine chest radiographic examination. The mass was observed again at age 33 years and was thought to be of neurogenic origin because of the long history. At this time, the patient also had two right retroperitoneal masses excised; reportedly, one was an intra-adrenal paraganglioma (pheochromocytoma) and the other a composite tumor with paraganglioma, neurofibroma, and ganglioneuroma. The histologic slides of these lesions were not available for review; however, the original pathologic description was clear and in particular located the

paraganglioma in an adrenal gland. The posterior mediastinal tumor was not mentioned again. Subsequently, the patient developed an anterior superior mediastinal paraganglioma that was excised at age 61 years. The patient's father (family 2, I.1) had lifelong cutaneous masses and was considered to have neurofibromatosis (molecular analysis was not performed). He died at age 90 years; there was no autopsy. One of his unaffected daughters (family 2, II.2) had similar lesions.

Unaffected Family Members

Thirty-six other primary relatives (parents, siblings, and children) of the affected patients did not manifest paraganglioma or gastric stromal sarcoma or other unusual findings and they were apparently unaffected. One (family 2, III.14) had amyotrophic lateral sclerosis. The parents (family 1, III.3 and III.8) of two affected patients were examined for the Carney triad and had negative results. Another apparently unaffected individual (family 5, III.3) was an obligate carrier.

DISCUSSION

In a prior report, three mechanisms were suggested as explanations for the occurrence of two components of the Carney triad (gastric stromal sarcoma and paraganglioma) in two unrelated young patients and the occurrence of paraganglioma (multicentric) in a sibling of each patient: the Carney triad was a familial condition; the combination of tumors was a specific (syndromic) concurrence of gastric stromal sarcoma and paraganglioma, independent of the Carney triad; and the tumors were unrelated, i.e., gastric stromal sarcoma occurred by chance in two patients with familial paraganglioma [Carney, 1999]. None of the explanations were considered satisfactory. First, components of the triad had not occurred in 355 parents, siblings, and children of the 77 other patients with the Carney triad; second, gastric stromal sarcoma had not occurred in any of the more than 115 kindreds reported with familial paraganglioma [Carney, 1999; Kohn et al., 1999; Lemaire et al., 1999; Lord and Chambers, 1999; de Krijger et al., 2000; Astuiti et al., 2001]; and third, the likelihood of the coincidental occurrence of gastric stromal sarcoma (multifocal) in more than one patient with familial paraganglioma (multicentric) seemed remote.

The additional findings in this study provide a unifying and satisfying explanation for the earlier puzzling and unexplained observations [Carney, 1999], namely, that there exists a previously unrecognized familial syndrome featuring paraganglioma and gastric stromal sarcoma (and possibly cutaneous soft tissue tumors as well). The findings point to a genetic, causal connection between the two tumors. The manner of transmission of the paragangliomas is compatible with autosomal dominant inheritance and incomplete penetrance. There was female-to-male transmission (family 4). Although gastric stromal sarcoma occurred in one member of each family only, its multifocal co-occurrence with paraganglioma in four patients seemed most unlikely to have occurred by chance. The cases of two young women with multiple gastric stromal sarcomas, one with ganglioneuroma [Lauwers et al., 1993] and the other with neuroblastoma [Johnston et al., 2001], may be relevant to syndromes discussed in this article.

It is not surprising that the paraganglioma–gastric stromal sarcoma syndrome was misdiagnosed as the Carney triad since the disorders share major components, feature tumors that are multicentric (paraganglioma) and multifocal (gastric stromal sarcoma), and usually become manifest in the first 3 decades of life. The former disorder does not feature pulmonary tumors, however, and lacks the female predilection of the Carney triad, and is familial. The two conditions now appear to be separate and distinct, although it is possible that they may be related molecularly. It is unlikely that the paraganglioma–gastric stromal sarcoma syndrome is related to the familial Carney complex (spotty skin pigmentation, myxomas, endocrine tumors [but not paraganglioma], and psammomatous melanotic schwannomas) [Carney et al., 1985; Carney, 1990; OMIM, 2001, #160980], even though psammomatous melanotic schwannoma, a very rare neoplasm, occurred (subsequent to the report) in a patient who had six siblings with paraganglioma [Zaslav et al., 1995].

Although there is overlap of components between the paraganglioma–gastric stromal sarcoma syndrome and the Carney triad, the relative frequency of the shared tumors in the two conditions is reversed: paraganglioma predominates in the syndrome whereas gastric stromal tumor predominates in the Carney triad. As a consequence, patients with the paraganglioma–gastric stromal sarcoma syndrome tended to be relatively symptomless, and the disorder came to the attention of the patient or physician as a result of the discovery of a mass, whereas patients with the Carney triad were regularly symptomatic because of the propensity of the gastric stromal sarcoma to cause anemia as a result of gastric bleeding. In patients with the paraganglioma–gastric stromal sarcoma syndrome who had gastric sarcoma, the sarcoma was symptomatic before the paraganglioma (four of five patients). Because of the generally symptomless nature of the paraganglioma associated with gastric stromal sarcoma, the tumor may have been present in at least some of the apparently unaffected relatives, one of whom (family 5, III.3) was an obligate carrier. It is less likely that the gastric stromal sarcoma was present and symptomless. The paragangliomas had a wider distribution than in PGL1, PGL2, and PGL3 and most of the functioning tumors were located in the retroperitoneum.

In 1903, Kohn [1903] suggested that a series of cell aggregates that included what we now recognize as the tympanic paraganglia, the carotid, vagal and aortic bodies, and organs of Zuckerkandl constituted a dispersed organ system, the paraganglionic system. The system includes the adrenal medulla, which is the largest paraganglion in the body. The cell aggregates are distributed in relation to the autonomic nervous system [Zak and Lawson, 1982], they store catecholamines and they are chromogranin-positive by

immunocytochemistry. The cytoplasm does not react with dichromate salts (as does that of cells of the adrenal medulla); hence, their designation nonchromaffin cells and tumors arising from them, nonchromaffin paragangliomas.

Paragangliomas are uncommon tumors. They may be familial or nonfamilial, nonfunctional or functional, intra- or extra-adrenal, and benign or malignant, and occur alone or accompanied by other disorders. At least 115 kindreds with the tumor involving 549 patients (290 male and 259 female) have been reported [Carney, 1999; Kohn et al., 1999; Lemaire et al., 1999; Lord and Chambers, 1999; de Krijger et al., 2000]; none had gastric stromal sarcoma, nor was the tumor reported in unaffected family members. Rarely, other conditions, including clotting defects [Kroll et al., 1964], angiolipomas [Lee et al., 1977], pituitary adenoma (one member of the family had a gastric leiomyoma) [Larraza-Hernandez et al., 1982], bony exostoses [Murphy et al., 1994], and sensorineural hearing loss [Lord and Chambers, 1999], have been coinherited with familial paraganglioma. In this regard, it will be recalled that a parent (family 2, I.1) of two affected individuals had cutaneous tumors that were interpreted as evidence of neurofibromatosis, a condition that was reported in an affected member of a PGL2 family [van Gils et al., 1992]. A member of both of these families had amyotrophic lateral sclerosis, one was affected and the other apparently unaffected. Familial carotid body tumors are inherited as an autosomal dominant trait with evidence for maternal imprinting in some families (Table II) [van der Mey et al., 1989; Baysal et al., 1997]. Often only siblings are affected and sometimes there are additional anatomical sites involved. Genetic loci for familial paragangliomas have been mapped to 11q22-23, 11q13.1, and 1q21—23 [Heutink et al., 1992; Mariman et al., 1995; Niemann et al., 2001]; in addition, mutations of the *SDHC*, *SDHD*, and *SDHB* genes belonging to the mitochondrial complex II have been identified in subgroups of patients with familial paraganglioma and familial pheochromocytoma [Baysal et al., 2000; Niemann and Muller, 2000; Astuiti et al., 2001; Taschner et al., 2001].

Gastric sarcomas are rare tumors. In the past, most were interpreted as leiomyosarcomas. A particular subtype, initially designated malignant leiomyoblastoma, then epithelioid leiomyosarcoma, was recently renamed stromal sarcoma when it was found to exhibit immunocytochemical markers for c-KIT and CD34 (but not those for smooth muscle) [Hirota et al., 1998; Sicar et al., 1999]. Histogenesis of the sarcoma has been linked to the interstitial cells of Cajal (gut pacemaker cells) [Perez-Atayade et al., 1993; Sicar et al., 1999]. Gain-of-function mutations of the *c-KIT* gene have been detected in both sporadic and inherited forms of gastric stromal sarcoma [Hirota et al., 1998; Nishida et al., 1998]. Inherited activating mutations are almost always associated with skin or mucosal hyperpigmentation or both in addition to the tumors [Marshall et al., 1990; Nishida et al., 1998]. Our findings indicate that gastric stromal sarcoma should be suspected in patients with familial paraganglioma who develop anemia due to gastrointestinal bleeding. Since gastric stromal sarcoma did not appear in one of our families until the affected member was 58 years old (average age of the other four patients with the sarcoma was 16 years),

TABLE II. Selected Data on Syndromic Paragangliomas*

Syndrome	OMIM number	Locus name	Gene locus	Gene	Inheritance	Paraganglia affected
Familial nonchromaffin paraganglioma	168000	PGL1	11q23	*SDHD*	AD[a]	Intercarotid, jugular, intravagal, tympanic; occasionally adrenal medulla
Familial nonchromaffin paraganglioma	601650	PGL2	11q13.1		AD[a]	Intercarotid, jugular, tympanic, and intravagal
Familial nonchromaffin paraganglioma	605373	PGL3	1q21-23	*SDHC*	AD	Intercarotid, tympanic, and jugular
Familial carotid body tumors and extra-adrenal pheochromocytomas	115310				AD	Intercarotid and retroperitoneal aorticosympathetic
Familial pheochromocytoma, familial pheochromocytoma and paraganglioma			1p35-p36	*SDHB*[b]	AD	Adrenal medulla, head and neck
von Hippel-Lindau disease	93300	VHL	3p26-p25	*VHL*	AD	Adrenal medulla; also extra-adrenal
Neurofibromatosis type I	162200	NF1	17q11.2	*NF1*	AD	Adrenal medulla; rarely extra-adrenal
Carney triad	604287				Not familial	Retroperitoneal aorticosympathetic, aortopulmonary body, intercarotid, and other neck; rarely adrenal medulla

*AD, autosomal dominant.
[a]Maternal imprinting.
[b]Rarely mutated in sporadic pheochromocytoma.

it is possible that an occasional reported family apparently with familial paraganglioma only may eventually manifest gastric stromal sarcoma.

Heretofore, we had accepted the occurrence of any two of the three major elements of the Carney triad in a patient as indicative of partial expression of the disorder and, although this may be true for some patients with the triad, the present study suggests in some instances the dyad of gastric stromal sarcoma and paraganglioma is a separate genetic syndrome inherited in an autosomal dominant manner. Thus, some of the 19 patients with this dyad of tumors who are now known to us as having the Carney triad may eventually be shown to have the familial paraganglioma–gastric stromal sarcoma syndrome. One of these patients, incidentally, had excision of a cutaneous angiolipoma and reportedly has pigmented skin spots, dolichocephaly, and arachnodactyly. Definitive diagnosis of these cases is not possible yet. This will have to await development in the patients of other components of the Carney triad (pulmonary chondroma or adrenal adenoma or possibly esophageal leiomyoma), occurrence of paraganglioma or gastric stromal sarcoma in a family member, or identification of the causative gene(s) of one or both syndromes.

Until the natural history of the paraganglioma–gastric stromal sarcoma syndrome is known, treatment of its component tumors should be based on their known behavior in the other syndromes in which they appear (PGL1, PGL2, and PGL3 and the Carney triad). Treatment of both tumors is therefore surgical. Functioning paragangliomas need to be excised. Nonfunctioning paragangliomas should also be excised, if feasible technically, because of the possibility of eventual compromise of important vascular and neural structures by continued growth of the tumors. Inoperable paragangliomas may be treated by radiation or particle embolization. Two of the patients we report had an encapsulated carotid body tumor that reportedly recurred. Recurrence of the usual carotid body tumor is exceptional unless the patient had multiple paragangliomas or familial paraganglioma or both [Nora et al., 1988]. Therefore, the two recurrent paragangliomas were most likely new neoplasms and not recurrences of incompletely excised tumors. The likelihood that a retroperitoneal paraganglioma in the paraganglioma–gastric stromal sarcoma syndrome will be in extra-adrenal location rather than intra-adrenal, and functioning, should be kept in mind. Gastric stromal sarcoma should be treated with gastrectomy with wide surgical margins because of the likelihood of the development of additional tumors in the gastric remnant. The outlook for the three patients in our report who had metastasis must be guarded. There has been no effective chemotherapy for the metastases of gastric stromal sarcoma until recently when tyrosine kinase inhibitor ST1571 (Glivec, Novartis, Basel, Switzerland) was used apparently successfully for their treatment [Joensuu et al., 2001]. Radiotherapy is ineffective for the sarcoma.

Patients with the paraganglioma–gastric stromal sarcoma syndrome should have genetic counseling. Follow-up of affected patients will vary with circumstance but may include clinical, laboratory, and radiographic examination for tumor recurrence or new tumor development or both. Patients who have partial gastrectomy should be examined for local recurrence of the gastric stromal sarcoma neoplasm at 3-year intervals. Family members who are apparently unaffected may be screened for the syndrome by means of the scheme (without search for pulmonary chondroma) suggested for Margulies and Sheps [1988] for the Carney triad.

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